Journal of the American College of Cardiology
© 2003 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 42, No. 4, 2003
ISSN 0735-1097/03/$30.00
doi:10.1016/S0735-1097(03)00787-3

# Brain Natriuretic Peptide and N-Terminal Brain Natriuretic Peptide in the Diagnosis of Heart Failure in Patients With Acute Shortness of Breath

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**OBJECTIVES** This study sought to compare the utility of measurement of plasma brain natriuretic peptide (BNP) and N-terminal brain natriuretic peptide (N-BNP) in the diagnosis of heart failure (HF) in patients with acute dyspnea.

**BACKGROUND** Plasma BNP is useful in differentiating HF from other causes of dyspnea in the emergency department. The N-terminal component of BNP has a longer half-life, and in HF increases in plasma N-BNP are proportionately greater.

**METHODS** We studied 205 patients (average age 70 ± 14 years) presenting to the emergency department with acute dyspnea. Brain natriuretic peptide was analyzed using a point-of-care test and two locally developed radioimmunoassays. N-terminal BNP was measured using a locally developed radioimmunoassay and a commercially available assay. Final diagnosis of HF was adjudicated by two cardiologists.

**RESULTS** Patients with HF (n = 70) had higher mean levels of both hormones by all assays ($p < 0.001$ for all). Results with all assays correlated closely (r values between 0.902 and 0.969). Subjects with left ventricular (LV) dysfunction or left-sided valvular disease but no HF had intermediate levels of BNP and N-BNP (lower than subjects with HF, and higher than subjects without HF with no LV dysfunction or left-sided valvular disease) ($p < 0.01$ for all). Using optimum cut-offs, specificity for the diagnosis of HF ranged between 70% and 89% (highest for the N-BNP assays). Sensitivity ranged between 80% and 94% (highest for the point-of-care BNP assay).

**CONCLUSIONS** Measurement of BNP or N-BNP is useful in the diagnosis of HF in acute dyspnea. Commercially available assays compare favorably with well-validated laboratory assays. Differences in sensitivity and specificity may influence the assay choice in this setting. (J Am Coll Cardiol 2003;42:728–35) © 2003 by the American College of Cardiology Foundation

Establishing the cause of shortness of breath in the acute setting can be difficult (1). Measurement of plasma brain natriuretic peptide (BNP), which is secreted by the heart in response to increases in transmural pressure, is useful in differentiating dyspnea due to heart failure (HF) from dyspnea related to other factors (2,3). Recently, point-of-care testing for plasma BNP has become available, and rapid measurement of BNP in the emergency department has been shown to be useful in establishing or excluding congestive HF in patients with acute dyspnea (4,5).

The amino-terminal fragment of BNP (N-BNP) circulates in human plasma. In health, N-BNP plasma levels are similar to those of BNP but increase more strikingly in HF (6,7). The ability of N-BNP measurement to aid in the diagnosis of HF in acutely breathless patients has not been assessed, and no study has compared measurement of BNP with that of N-BNP in the diagnosis of HF in dyspneic patients. An automated commercial assay for N-BNP (Roche Diagnostics, Basel, Switzerland) has recently become available.

This study was designed to compare the utility of measurements of BNP and N-BNP in the diagnosis of HF in acutely short-of-breath patients using a point-of-care BNP test (Biosite Diagnostics, San Diego, California) and a commercially available automated N-terminal BNP assay (Roche Diagnostics) and, in addition, to compare these assays with locally developed, well-validated radioimmunoassays for BNP and N-BNP.

## METHODS

The protocol was approved by the Ethics Committee of the Canterbury District Health Board, and participants gave informed consent. Two hundred and five patients with dyspnea presenting to the local emergency department were enrolled. Patients were eligible for enrollment if dyspnea was part of the reason for presentation and they were able to give a blood sample within 8 h of arrival in the emergency department. Data collected included results of medical history and physical examination, blood tests, chest X-ray, and other diagnostic tests. Echocardiograms were undertaken as part of the standard clinical assessment in 171 patients, and an additional five patients had radionuclide ventriculography.

From the Department of Medicine, Christchurch School of Medicine, University of Otago, Christchurch, New Zealand. This work was supported by the Health Research Council of New Zealand and the National Heart Foundation of New Zealand. Triage BNP test strips and analyser were provided by Biosite Diagnostics. Dr. Gottlieb C. Friesinger, II acted as Guest Editor for this manuscript. John Lainchbury holds a National Heart Foundation Senior Fellowship. Mark Richards holds the National Heart Foundation Chair of Cardiovascular Studies.

Manuscript received February 4, 2003; revised manuscript received March 27, 2003, accepted May 12, 2003.

**Abbreviations and Acronyms**

BNP = brain natriuretic peptide
CNP = C-type natriuretic peptide
HF = heart failure
LV = left ventricular
N-BNP = N-terminal brain natriuretic peptide

The final determination of the actual diagnosis was made by two independent cardiologists who had access to all relevant medical records, except the results of the natriuretic peptide assays. The information available included emergency department and inpatient medical records and results of all investigations. The principles for diagnosis of HF contained in the European Society of Cardiology guidelines were followed (8), and all patients with HF fulfilled Framingham congestive HF score criteria. In cases of disagreement (n = 18), a third cardiologist was the final adjudicator.

Blood samples were collected into EDTA tubes, and a sample was used immediately for analysis in the point-of-care BNP test. The rest of the sample was placed immediately on ice, centrifuged within 30 min at 4°C, and the plasma was stored at −80°C before assay.

The locally developed radioimmunoassays for N-BNP and BNP were performed on extracted plasma. Plasma was loaded on C18 reverse phase Sep-Pak cartridges, washed with 6 ml of 0.1% trifluoroacetic acid and eluted with 2 ml of 80% isopropanol in water. The extract was dried under an air stream and reconstituted in buffer.

For N-BNP radioimmunoassay 100 μl was incubated with 100 μl of radiolabeled N-BNP (amino acids 1-15 of N-BNP) and 100 μl of antiserum raised against N-BNP (amino acids 1-15 N-BNP). After incubation for 24 h at 4°C, bound and free peptide was separated with a solid phase second antibody reagent (SacCell donkey anti rabbit) and the bound radioactivity counted in a gamma counter (6). Within assay coefficients of variation were <50 pmol/l, 11.6%; 50 to 200 pmol/l, 3.9%; >200 pmol/l, 3.4%. Between assay coefficients of variation were 11 pmol/l, 17.2%; 72 pmol/l, 8.5%; 139 pmol/l, 7.6%.

N-terminal brain natriuretic peptide was also measured with a Roche Diagnostics proBNP assay on an Elecsys 2010 analyser. In this two-site assay 20 μl of sample is incubated with biotinylated polyclonal antibody plus a different polyclonal antibody labeled with a ruthenium complex. Both antibodies are directed to the proBNP (amino acids 1-76 of proBNP) region. Following incubation the bound fraction is separated with streptavidin-coated microparticles and quantitated by chemiluminescence. Data provided by Roche Diagnostics show total assay precision ranges from 1.8% at 800 pmol/l to 2.7% at 20.7 pmol/l and the detection limit is 0.6 pmol/l. Crossreactivity with other peptides including BNP, amino-terminal proANP peptides, C-type natriuretic peptide (CNP), and components of the renin-angiotensin system were all <0.001%.

Brain natriuretic peptide was measured using two locally developed radioimmunoassays. The first assay was designed for research measurements (Research BNP), and the second to provide more rapid results for clinical use (Clinical BNP).

For the Research BNP assay standard or extract (100 μl) was added to assay tubes plus 100 μl of BNP antiserum (Peninsula Laboratories, San Carlos, California) (9). The assay was incubated for 22 to 24 h at 4°C, after which 100 μl of $^{125}$I labeled BNP (10,000 cpm) was added and incubated at 4°C for 22 to 24 h. Bound and free BNP were separated using a solid phase second antibody method in which 1 ml of 5% Sac-Cel (IDS, Boldon, United Kingdom) plus 5% Dextran in assay buffer was added and then centrifuged after 30 min at room temperature. The pellet was then counted in a gamma counter.

The BNP antiserum had the following crossreactivities (supplied by the manufacturer): BNP-32 (Human) 100%; ANP1-28 (Human) <0.001%; BNP-26 (porcine) <0.001%; cANP (amino acids 4-23 of cANP) <0.007%.

Using this method, recoveries of BNP from human plasma were 71% at 44 pmol/l, and 70% at 40 and 80 pmol/l. The assay had a mean detection limit of 0.75 pmol/l after extraction when calculated over 30 assays. The between assay coefficients of variation were 21.6% at 3.5 pmol/l, 17.6% at 6.7 pmol/l, and 17% at 21 pmol/l when measured over 30 assays.

The Clinical BNP assay was identical to the Research BNP assay except for substitution of a 3-h preincubation with antibody at room temperature for the 22- to 24-h preincubation at 4°C before addition of radiolabeled tracer and a reduction in the second incubation time to 17 to 18 h at 4°C (10). This change was effected to provide a rapid assay that would deliver clinical results within 24 h but with consequent lower sensitivity (higher detection limit) and slightly higher set results brought about by the altered incubation conditions.

Using this method, recoveries of BNP from human plasma were 83% at 44 pmol/l. The assay had a mean detection limit of 2.5 pmol/l after extraction and between assay coefficients of variation were 10.8% at 24 pmol/l and 12.1% at 45 pmol/l when measured over 36 assays.

Brain natriuretic peptide was also measured with the point-of-care Triage BNP Test (Biosite Diagnostics Inc., San Diego, California). Blood is added to a small test strip, which filters out blood cells. The plasma moves by capillary action into a reaction chamber where it is mixed and incubated with fluorescent-labeled antibodies. Brain natriuretic peptide bound to labeled antibody is trapped further along the capillary and quantified by fluorescence measurement in a small reader. Data supplied by Biosite Diagnostics show the recovery of BNP added to plasma ranges from 86% to 105%, with a detection limit of 1.4 pmol/l. Coefficients of variation (total imprecision) ranged from 10.1% at 8.3 pmol/l to 16.2% at 312 pmol/l. The assay did not cross-react with atrial natriuretic peptide, CNP, N-ANP, or N-BNP peptides, or angiotensin peptides.

**Table 1.** Patient Characteristics (n = 205)

| Characteristic | Mean Age 70 ± 14 Years |
|---|---|
| Male | 100 (49%) |
| Coronary disease | 88 (43%) |
| Previous heart failure | 52 (25%) |
| COPD | 86 (42%) |
| NYHA | |
| II | II (12%) |
| III | III (30%) |
| IV | IV (58%) |
| Orthopnea | 83 (41%) |
| PND | 29 (14%) |
| Elevated JVP | 63 (31%) |
| Rales | 98 (48%) |
| Third heart sound | 24 (12%) |
| Bilateral ankle edema | 67 (33%) |

COPD = chronic obstructive pulmonary disease; JVP = jugular venous pressure; NYHA = New York Heart Association functional class; PND = paroxysmal nocturnal dyspnea.

**Statistical analysis.** Comparisons between assay results were determined by unpaired and paired *t* tests, as appropriate. Pearson's correlation coefficients between assays were determined on log transformed data. To determine the capacity of measurements of BNP and N-BNP to differentiate HF from other causes of dyspnea, we undertook receiver-operating characteristic curve analysis and determined optimum cut-offs for sensitivity, specificity, positive and negative predictive value, overall accuracy of the test, and area under the receiver-operating characteristic curves.

We performed a stepwise multivariate logistic regression analysis for each of the five assays used, to determine the ability of BNP/N-BNP measurements to provide diagnostic information in addition to standard clinical variables. For all analyses, $p < 0.05$ was considered statistically significant.

## RESULTS

The characteristics of 205 patients are shown in Table 1. All patients had shortness of breath as part of their reason for presenting to the emergency department. The final diagnosis was HF in 70 patients (34%). The final clinical diagnosis for the remaining 135 patients without HF is given in Table 2.

Figure 1 presents the BNP and N-BNP values for the patients with and without HF. For all assays, patients with HF had significantly higher plasma levels of the measured hormone ($p < 0.001$ for all). Thirty of the patients with HF had a left ventricular (LV) ejection fraction ≥45%, and in this group the hormone levels by each assay were significantly less than in those with HF and LV ejection fraction <45 but significantly higher than in those without HF ($p < 0.05$ for all).

Twenty-three subjects were found to have significant LV dysfunction or left-sided valvular disease (defined as a LV

**Table 2.** Final Clinical Diagnosis in 135 Patients Without Heart Failure

| | n |
|---|---|
| COPD | 45 |
| Pneumonia | 18 |
| Asthma | 19 |
| Complications of carcinoma of the lung | 9 |
| Pulmonary embolism | 3 |
| Interstitial lung disease | 5 |
| Other* | 36 |

*Other includes dyspnea associated with cardiac ischemia, anxiety, anemia, thyrotoxicosis, undiagnosed and musculoskeletal chest pain, periearditis, and patients with no definite final clinical diagnosis.

COPD = chronic obstructive pulmonary disease.

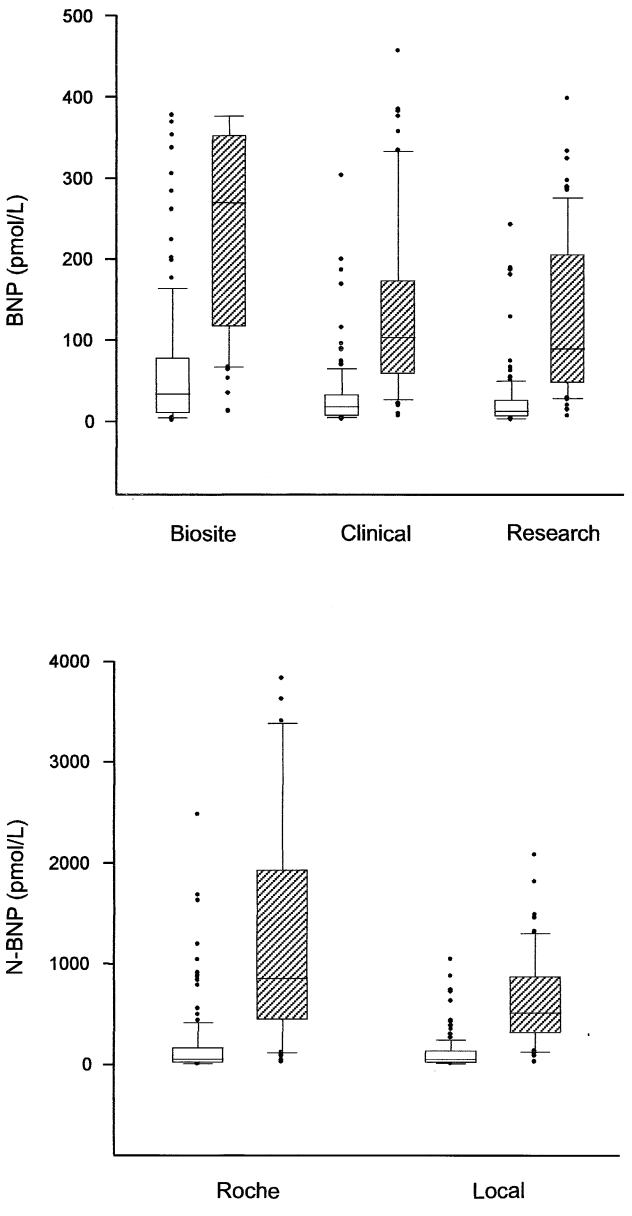



**Figure 1.** Brain natriuretic peptide (BNP) and N-terminal BNP (N-BNP) values by five different assays in 135 subjects without heart failure **(open bars)** and 70 patients with heart failure **(striped bars)**. Values were significantly higher by all assays for those with heart failure ($p < 0.001$ for all). Biosite = Biosite point-of-care BNP assay; Clinical = local clinical BNP assay; Research = local research BNP assay; Roche = Roche N-BNP assay; Local = local N-BNP assay. **Bars** indicate median value and interquartile range, **lines** represent 10th and 90th percentile values, **dots** represent outlying values.

ejection fraction <45% or ≥grade 3/4 mitral or aortic regurgitation, or aortic stenosis with a peak Doppler-derived gradient >50 mm Hg) but were considered not to have HF as a cause for their acute dyspnea. In this group of patients, values of BNP or N-BNP by all assays were significantly higher than those from the group with no HF and no LV systolic dysfunction or significant left-sided valvular disease, and were significantly less by all assays than the results from those with definite HF (Fig. 2) ($p < 0.05$ for all comparisons). In these 23 patients, the final clinical diagnoses were chronic obstructive pulmonary disease (n = 7), pneumonia (n = 4), pulmonary thromboembolism (n = 2), interstitial lung disease (n = 2), asthma (n = 1), and other diagnoses (n = 7).

There were close correlations between all of the five assays, ranging from an r value of 0.902 (for Biosite BNP vs. Roche N-BNP results) to an r value of 0.969 (Roche N-BNP vs. local N-BNP assay results) (Fig. 3) (p value for correlations between all the assays was <0.0001). Correlations between the Biosite BNP assay and the Clinical BNP assay gave an r value of 0.911, and between the Biosite BNP assay and the Research BNP assay an r value of 0.916 ($p < 0.0001$ for both). There were significant correlations between age and the results of all assays with r values ranging from 0.58 for age versus local research BNP assay results to 0.636 for age versus local N-BNP results ($p < 0.01$ for all comparisons). The correlations between age and hormone level was not significant among those with HF, but remained significant for all assays among those without HF ($p < 0.05$). In addition, there were significant inverse relationships between ejection fraction and the results of all assays with r values ranging from −0.45 for Biosite versus ejection fraction up to −0.53 for local research BNP versus ejection fraction ($p < 0.01$ for all comparisons). There were no significant gender differences between hormone levels for any of the assays.

Nineteen patients without HF had echocardiographically derived tricuspid regurgitant velocities >3 m/s (average 3.5 m/s) yielding an estimated right ventricular systolic pressure of 36 mm Hg greater than mean right atrial pressure, and chronic obstructive pulmonary disease with an otherwise structurally normal left ventricle. Hormone results from these 19 subjects by all assays did not significantly differ from the rest of the subjects without HF ($p > 0.05$ for all comparisons).

In multivariate models incorporating clinical parameters (age, history of previous HF, presence of coronary artery disease, elevated jugular venous pressure, rales, ankle edema, and chest X-ray features of HF), hormone concentrations by all assays remained significantly and independently predictive of the final diagnosis of HF with $p < 0.005$ for all assays. Other clinical parameters that remained significantly predictive of a final diagnosis of HF were history of previous HF, peripheral edema, and chest X-ray evidence of HF in all models ($p < 0.05$ for all).

Figure 4 illustrates receiver-operating characteristic

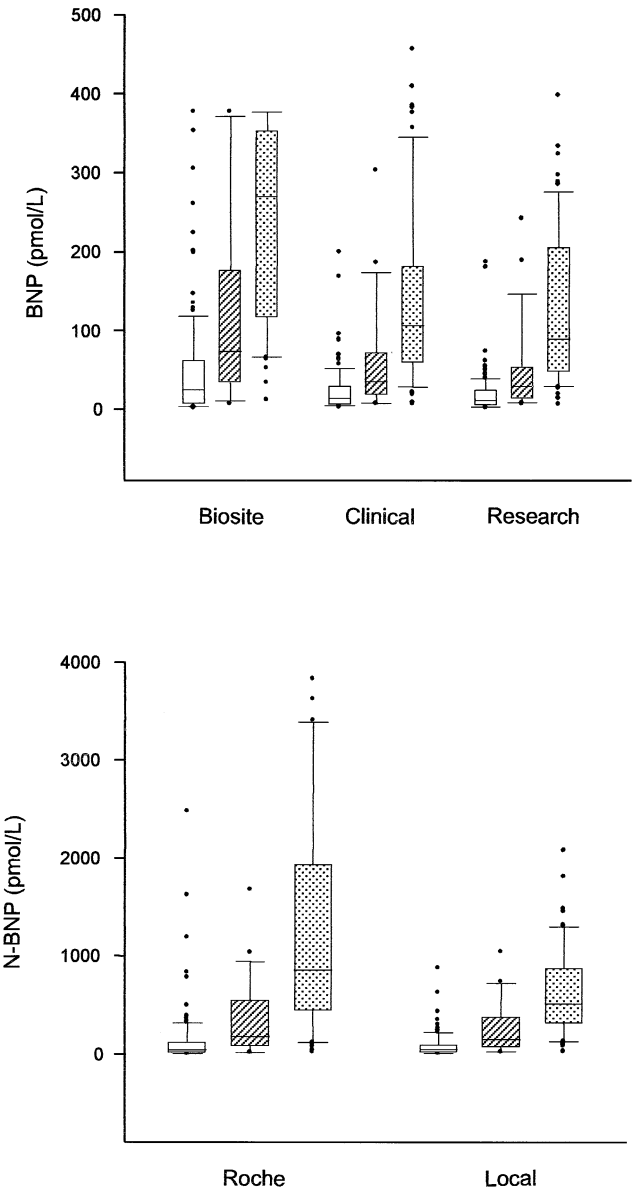



**Figure 2.** Brain natriuretic peptide (BNP) and N-terminal BNP (N-BNP) results from five different assays in 112 patients with no heart failure **(open bars)**, 23 patients with no heart failure but significant left ventricular systolic dysfunction or left-sided valvular disease **(striped bars)**, and 70 patients with congestive heart failure **(dotted bars)**. By all assays, results from the group with significant left ventricular dysfunction or left-sided valvular disease and no heart failure were significantly higher than those without heart failure and significantly less than those with heart failure ($p < 0.01$ for all comparisons). Biosite = Biosite point-of-care BNP assay; Clinical = local clinical BNP assay; Research = local research BNP assay; Roche = Roche N-BNP assay; Local = local N-BNP assay. **Bars** indicate median value and interquartile range, **lines** represent 10th and 90th percentile values, **dots** represent outlying values.

curves for each of the five assays. The arrow indicates the value for optimum sensitivity and specificity. Specificity at optimum values was lowest with the Biosite BNP assay at 70% and highest for the local N-BNP assay at 89%. Sensitivity was greatest with the Biosite BNP assay at 94% and lowest with the Roche N-BNP assay at 80%. In general, specificity appeared to be highest with the N-BNP assays,

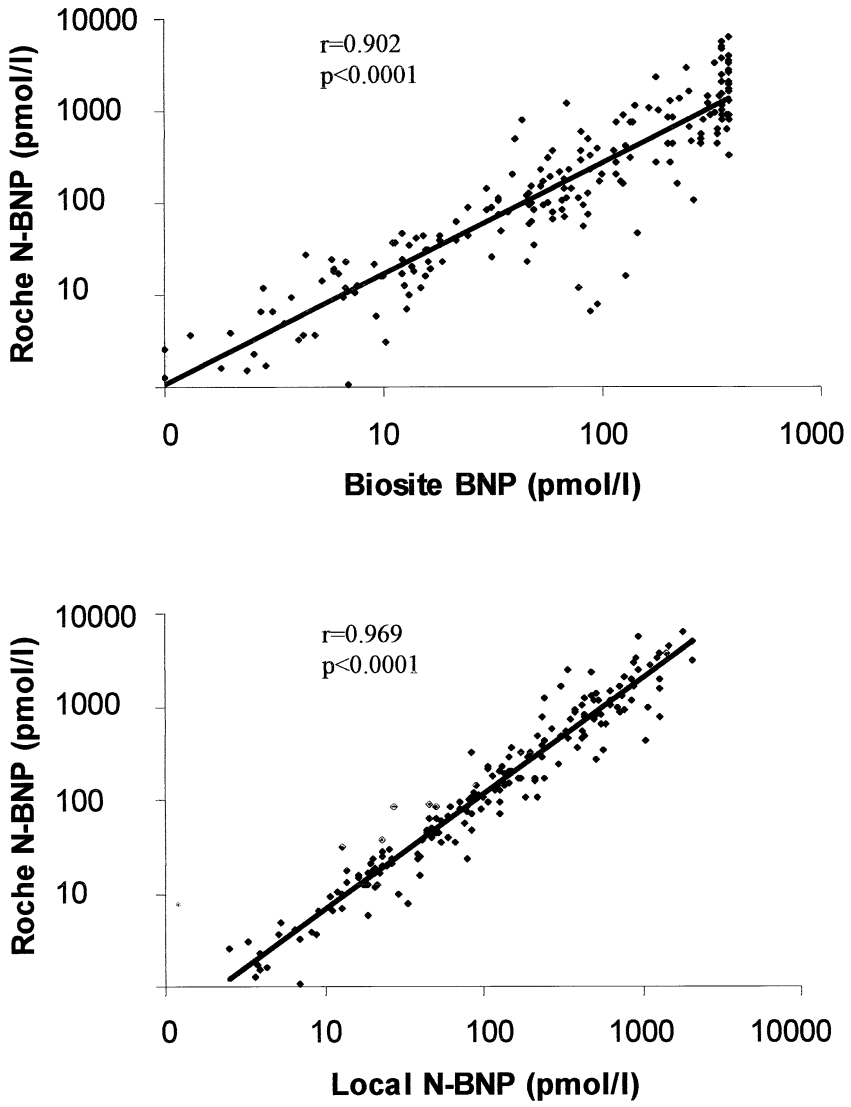


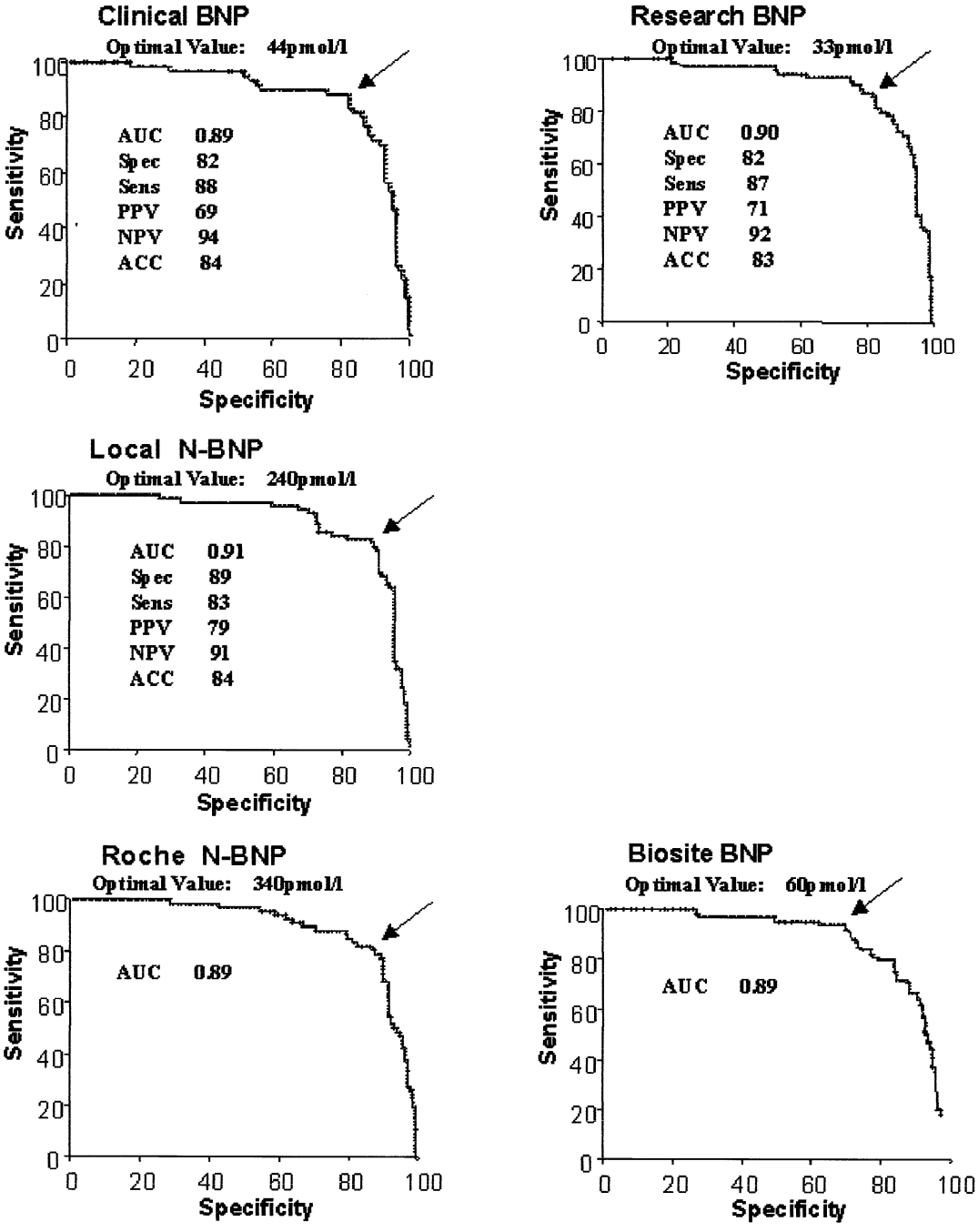

**Figure 3.** Correlation between the results of the Roche N-terminal brain natriuretic peptide (N-BNP) assay and the Biosite brain natriuretic peptide (BNP) assay **(top)** and Roche N-BNP assay and Local N-BNP assay **(bottom)**. The assay results are log transformed. Biosite BNP = Biosite point-of-care BNP assay; Roche N-BNP = Roche N-BNP assay; Local N-BNP = local N-BNP assay.

although sensitivity was greater with the BNP assays. Positive predictive values ranged from 62% with the Biosite BNP assay to 79% with the local N-BNP assay, whereas negative predictive values were uniformly 90% or greater, being highest with the Biosite BNP assay at 96%. For both commercially available assays, a range of values and the associated specificity, sensitivity, positive and negative predictive values, and accuracy are given in Figure 4.

## DISCUSSION

Our findings confirm that measurement of BNP is useful in the diagnosis of HF in patients presenting to the emergency department with shortness of breath (4,5). In addition, our study demonstrates that plasma N-BNP is also useful in this setting.

Across the five assays in this study, there was some variability in the sensitivity and specificity. The point-of-care Biosite BNP test yielded the highest sensitivity (94%) and a somewhat lower specificity (70%) at the optimum cut-off value. A point-of-care test with these characteristics in the acute care setting allows a low result to confidently exclude HF. In our study a value <60 pmol/l (208 pg/ml) had a negative predictive value of 96%. In the previous multicenter study by Maisel et al. (5), 1,586 patients presenting to the emergency department with acute dyspnea had point-of-care BNP measured, and in that population an optimum cut-off of 34 pmol/l (100 pg/ml) was obtained (sensitivity of 90% and a specificity of 76%). In the current study, a value of 34 pmol/l (100 pg/ml) had higher sensitivity (97%) but lower specificity (49%). The optimum cut-off values and characteristics of the tests between the two studies vary and likely relate to differences in the




| Roche N-BNP (pmol/L) | Spec | Sens | PPV | NPV | ACC |
|---|---|---|---|---|---|
| 140 | 71 | 87 | 60 | 91 | 76 |
| 240 | 82 | 83 | 70 | 90 | 83 |
| **340** | **87** | **80** | **76** | **89** | **85** |
| 440 | 90 | 74 | 79 | 87 | 85 |
| 540 | 92 | 68 | 80 | 84 | 84 |

| Biosite BNP (pmol/L) | (pg/ml) | Spec | Sens | PPV | NPV | ACC |
|---|---|---|---|---|---|---|
| 20 | 69 | 44 | 97 | 47 | 97 | 62 |
| 30 | 104 | 49 | 97 | 49 | 97 | 65 |
| **60** | **208** | **70** | **94** | **61** | **96** | **78** |
| 80 | 277 | 78 | 83 | 65 | 90 | 79 |
| 100 | 346 | 84 | 77 | 71 | 88 | 82 |

**Figure 4.** Receiver-operating characteristic curves for the five assays for the diagnosis of heart failure. A range of cut-off values for the commercially available Biosite brain natriuretic peptide (BNP) and Roche N-terminal brain natriuretic peptide (N-BNP) assays are given at the bottom of the figure; the highlighted row represents the optimal value for specificity and sensitivity. ACC = overall accuracy of the test; AUC = area under the receiver-operating characteristic curve; NPV = negative predictive value; PPV = positive predictive value; Spec = specificity; Sens = sensitivity. The **arrows** indicate the optimum value for cut-off for specificity and sensitivity, defined as the point geometrically closest to perfect sensitivity and specificity. Overall accuracy of the test is defined as the percentage of patients correctly classified as having heart failure or not. Clinical BNP = local clinical BNP assay; Biosite BNP = Biosite point-of-care BNP assay; Research BNP = local research BNP assay; Roche N-BNP = Roche N-BNP assay; Local N-BNP = local N-BNP assay.

underlying populations. In particular, the average age of our population was six years older than in the Maisel study (5). These results emphasize the need to be aware of both the variability of test performance across different populations and the way in which test characteristics vary depending on the chosen cut-off value.

N-terminal BNP increases more strikingly in HF than does BNP and has a longer half-life (7,11). These features could influence the diagnostic utility of measurement of N-BNP in acutely short-of-breath patients. Both N-BNP assays had somewhat higher specificity than the BNP assays, while maintaining sensitivities of greater than 80%. Given the longer plasma half-life of N-BNP, its diagnostic utility may be influenced by duration of symptoms, and it may be less affected by acute treatment, such as administration of diuretics. Further study is required to clarify these issues.

Close correlations were observed between results from the individual assays. Our own radioimmunoassays for both BNP and N-BNP are well established and validated (6,9,10). The close correlations between the results of the two commercially available automated assays and our laboratory assays provide support for the use of the commercial assays in hospitals without extensive experience in measurement of plasma peptides. A previous study by Fischer et al. (12) has also noted close correlation between results of the Biosite and Roche assays in a group of 50 normal subjects and 100 patients with suspected HF.

As expected, there was a correlation between ejection fraction and hormone level, and plasma levels of BNP are known to reflect the severity of underlying cardiac dysfunction (13,14). A correlation between age and natriuretic peptide levels has been previously noted (15), and this was confirmed in the current study. This may be important for the clinical application of BNP tests, and further studies with larger numbers of subjects will be necessary to determine whether adjustment of optimum thresholds for the diagnosis of HF are necessary based on age.

Maisel et al. (5) have previously shown that subjects with LV dysfunction but without HF have values of plasma BNP intermediate between those of patients with no HF and normal LV function and those with shortness of breath due to HF. This is confirmed in our current study, but we included subjects with significant left-sided valvular disease and no HF, along with significant LV dysfunction and no HF, and found similar results. This may be clinically useful in that subjects who are thought not to have HF but have intermediate values of natriuretic peptides may require further assessment for possible previously unrecognized underlying structural cardiac disease.

In the acute setting, echocardiography is frequently not available and the diagnosis of HF rests on clinical assessment and chest X-ray (16). Multivariate analysis in the current study suggests measurement of BNP and N-BNP contributes significantly to the ability to diagnose HF. The Biosite assay has the advantage of point-of-care applicability; however, the commercially available Roche N-BNP assay is available through an automated system, which can give rapid turnaround times for results and run a large number of samples simultaneously. The clinical application of these and other commercial assays (which may become available) will require care to avoid confusion resulting from the different hormones measured and different cut-off values suggested for the diagnosis of HF.

A significant number of patients had chronic obstructive pulmonary disease and a number of these had a degree of pulmonary hypertension without right HF, as demonstrated by tricuspid regurgitant velocity measurement at echocardiography. These patients did not have significantly elevated levels of BNP or N-BNP. Increases in natriuretic peptide plasma concentrations had been reported in subjects with pulmonary hypertension compared with normal subjects, but in the current study the levels were compared with those in other unwell subjects with dyspnea (17). Numbers were small but suggest that assessment of BNP is useful in differentiating HF from chronic obstructive pulmonary disease even in the presence of a degree of pulmonary hypertension.

**Conclusions.** Our results support the use of BNP and N-BNP measurement in the assessment of patients presenting to hospital with shortness of breath. The commercially available assays compare favorably with well-validated laboratory assays. The Biosite assay may be most useful in excluding HF in this population, a useful characteristic in a point-of-care test. N-terminal brain natriuretic peptide assays appear to have somewhat better specificity and positive predictive value.

### Acknowledgment

We acknowledge Barbara Griffin for providing secretarial assistance.

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## REFERENCES

1. Remes J, Miettinen H, Reunanen A, et al. Validity of clinical diagnosis of heart failure in a primary care setting. Eur Heart J 1991;12:315–21.
2. Levin ER, Gardner DG, Samson WK. Natriuretic peptides. N Engl J Med 1998;339:321–8.
3. Davis M, Espiner E, Richards G, et al. Plasma brain natriuretic peptide in assessment of acute dyspnoea. Lancet 1994;343:440–4.
4. Dao Q, Krishnaswamy P, Kazanegra R, et al. Utility of B-type natriuretic peptide in the diagnosis of congestive heart failure in an urgent-care setting. J Am Coll Cardiol 2001;37:379–85.
5. Maisel AS, Krishnaswamy P, Nowak RM, et al. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. N Engl J Med 2002;347:161–7.
6. Hunt PJ, Yandle TG, Nicholls MG, et al. The amino-terminal portion of pro-brain natriuretic peptide (pro-BNP) circulates in human plasma. Biochem Biophys Res Commun 1995;214:1175–83.
7. Hunt PJ, Richards AM, Nicholls MG, et al. Immunoreactive amino-

terminal pro-brain natriuretic peptide (NT-PROBNP): a new marker of cardiac impairment. Clin Endocrinol 1997;47:287–96.
8. Remme WJ, Swedberg K, Task Force for the Diagnosis and Treatment of Chronic Heart Failure, European Society of Cardiology. Guidelines for the diagnosis and treatment of chronic heart failure. Eur Heart J 2001;22:1527–60.
9. Yandle TG, Richards AM, Gilbert A, et al. Assay of brain natriuretic peptide (BNP) in human plasma: evidence for high molecular weight BNP as a major plasma component in heart failure. J Clin Endocrinol Metab 1993;76:832–8.
10. Fleischer D, Espiner EA, Yandle TG, et al. Rapid assay of plasma brain natriuretic peptide in the assessment of acute dyspnoea. N Z Med J 1997;110:71–4.
11. Pemberton CJ, Johnson ML, Yandle TG, et al. Deconvolution analysis of cardiac natriuretic peptides during acute volume overload. Hypertension 2000;36:355–9.
12. Fischer Y, Filzmaier K, Stiegler H, et al. Evaluation of a new, rapid bedside test for quantitative determination of B-type natriuretic peptide. Clin Chem 2001;47:591–4.
13. Richards AM, Nicholls MG, Yandle TG, et al. Plasma N-terminal pro-brain natriuretic peptide and adrenomedullin: new neurohormonal predictors of left ventricular function and prognosis after myocardial infarction. Circulation 1998;97:1921–9.
14. Omland T, Aakvaag A, Bonarjee VVS, et al. Plasma brain natriuretic peptide as an indicator of left ventricular systolic function and long-term survival after acute myocardial infarction. Comparisons with plasma atrial natriuretic peptide and N-terminal proatrial natriuretic peptide. Circulation 1996;93:1963–9.
15. Redfield MM, Rodeheffer RJ, Jacobsen SJ, et al. Plasma brain natriuretic peptide concentration: impact of age and gender. J Am Coll Cardiol 2002;40:976–82.
16. Stevenson LW, Perloff JK. The limited reliability of physical signs for estimating hemodynamics in chronic heart failure. JAMA 1989;261: 884–8.
17. Nagaya N, Nishikimi T, Uematsu M, et al. Plasma brain natriuretic peptide as a prognostic indicator in patients with primary pulmonary hypertension. Circulation 2000;102:865–70.